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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Mehran Khodadoust	Confirmation No.:	6131
Serial No.:	10/029,471	Art Unit:	1636
Filed:	October 25, 2001	Examiner:	Michele K. Joike
Customer No.:	21559		
Title:	COMPOSITIONS AND METHODS FOR THE DISCOVERY AND SELECTION OF BIOLOGICAL INFORMATION		

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AMENDED BRIEF ON APPEAL

In support of Appellant's Notice of Appeal and the Pre-Appeal Brief Request for Review that was filed in connection with the above-captioned case on February 11, 2008, and with reference to the Office Action that was mailed in this case on September 10, 2007, and the Panel Decision of Pre-Appeal Brief that issued on April 1, 2008, submitted herewith is Appellant's Appeal Brief. This brief has been amended to reflect the change in the real party in interest.

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Real Party in Interest

The real party in interest in this case is Bionaut Pharmaceuticals Inc., to whom all interest in the present application has been assigned. A copy of the assignment is provided herewith.

Related Appeals and Interferences

There are no pending appeals or interferences related to this case.

Status of Claims

Claims 1-82 have been cancelled. Claims 83-109 are pending. Claims 83, 84, and 88-96 stand rejected under 35 U.S.C. § 102(b). Claims 85-87 and 97-109 stand rejected under 35 U.S.C. § 103(a). Claims 83-109 are on appeal.

Status of Amendments

All amendments have been entered and are reflected in the appended claims.

Summary of Claimed Subject Matter

Appellant's invention features novel nucleic acid molecules which include three selection markers all of which lack a promoter and, when integrated into the genome of a cell, are responsive to one or more endogenous regulatory elements in that cell.

Appellant has discovered that the linkage of three markers to endogenous regulatory elements of the host cellular gene is particularly advantageous because it allows for rapid development of cellular assays in which activity of the regulated genetic site can be measured quantitatively. Having the positive and negative selection markers responsive to one or more endogenous regulatory elements allows for the selection of cells in which the nucleic acid has integrated into an active genetic site. Having the reporter gene responsive to one or more endogenous regulatory elements allows for a quantitative read-out of the activity at the active genetic site, for example, after stimulation with an agent that stimulates activity of the regulatory element.

Appellant's invention is reflected in claims 83-109. Independent claim 83 and dependent claims 84-96 are directed to a nucleic acid that includes a negative selection marker, a positive selection marker, and a reporter gene, all three of which are promotorless and responsive to one or more endogenous regulatory elements in a cell after integration of the nucleic acid into the cell. Dependent claims 92 and 95 recite a vector and a cell, respectively, having the nucleic acid of claims 83, 84, or 85. The invention of claims 83-96 is described throughout the specification, for example, at page 6, line 15 to page 7, line 10; page 10, lines 5-13; page 11, line 14 to page 12, line 3; page 23, lines 3-8 and 11-16; page 27, lines 23-24 and line 30 to page 28, line 3; page 32, lines 13-16; page 38, line 27 to page 39, line 16, and in Figure 8A.

Independent claim 97 is directed to a vector that includes a nucleic acid segment

having a positive selection marker, negative selection marker, and a nucleic acid encoding a transactivator polypeptide wherein, when integrated into the genome of a cell, all three elements are responsive to one or more endogenous regulatory elements in the cell.

Independent claim 109 is directed to a cell that includes a cassette having a positive selection marker, a negative selection marker, and a nucleic acid encoding a transactivator polypeptide, all three of which are promotorless and responsive to one or more endogenous regulatory elements in the cell. The cell also includes a nucleic acid having a promoter operably linked to an element that is directly response to the transactivator polypeptide in the cassette.

The invention of claims 97-109 is described throughout the specification, for example, at page 10, line 14 to page 12, line 3; page 17, line 24 to page 18, line 20; page 24, lines 11-16; page 25, lines 8-16; and in Figures 2 and 5.

Grounds of Rejection to be Reviewed on Appeal

This appeal presents two issues:

1. Whether the Examiner erred in rejecting claims 83, 84, and 88-96 under 35 U.S.C. § 102(b) for anticipation by Baetscher et al., U.S.P.N. 5,922,601 (hereafter referred to as "Baetscher").

2. Whether the Examiner erred in rejecting claims 85-87 and 97-109 under 35 U.S.C. § 103 for obviousness over Baetscher in view of MPEP § 2144.04 (VI)(C),

Zambrowicz et al., U.S.P.N. 6,436,707 (hereafter referred to as "Zambrowicz"), or Massie et al. (*J. Virology* 72:2289-2296 (1998); hereafter referred to as "Massie").

Argument

1. The Novelty Rejection

The Legal Standard For Anticipation Under 35 U.S.C. § 102(b)

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros., Inc. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). *See also EMI Group North America, Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342, 1350 (Fed. Cir. 2001).

"A single reference must describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art." *Verve, LLV v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002). *See also Crown Operations Int'l, Ltd.*, 289 F.3d at 1357 ("An anticipating reference must describe the patented subject matter with sufficient clarity and detail to establish that the subject matter existed in the prior art and that such existence would be recognized by persons of ordinary skill in the field of the invention."); MPEP § 2131 ("The identical invention must be shown in as complete detail as is contained in the claim.").

Claims 83, 84, and 88-96 Are Not Anticipated by Baetscher

Claims 83, 84, and 88-96 stand rejected under 35 U.S.C. § 102(b) for anticipation by Baetscher. Baetscher does not teach all of the limitations of the claims, and the Examiner has mischaracterized the teachings of Baetscher. Appellant separately addresses this ground of rejection as it applies to independent claim 83 and dependent claims 84 and 88-96 and as it applies to dependent claims 95-96.

Claims 83, 84, and 88-94

Claim 83 and dependent claims 84 and 88-94 are directed to nucleic acids and vectors that include promoterless constructs. Representative claim 83 is reproduced below.

> 83. A nucleic acid including:
> (a) a splice acceptor site;
> (b) a cassette including in any order a negative selection marker, a positive selection marker, and a reporter gene, wherein said negative selection marker, said positive selection maker, and said reporter gene are integrated into the genome of at least one cell and responsive to one or more endogenous regulatory elements in said at least one cell after said nucleic acid is contacted with a cell.

In rejecting claim 83, the Examiner asserts that,

> Baetscher teaches integration of promoterless positive and negative selection markers (columns 4-6). Specifically a vector containing promoterless markers, including positive and negative selection markers, is integrated into the genome of a cell. The markers are promoterless so that once integrated, they are under control of an endogenous regulatory

element." (Page 3, Office Action mailed on September 10, 2007; "the 2007 Office Action".)

For the following reasons, this conclusion mischaracterizes the Baetscher reference.

Baetscher never teaches a construct having a negative selection marker, positive selection marker, and reporter gene under the control of a host cellular promoter. Instead, Baetscher's constructs that include two selection markers and a reporter gene include a promoter element regulating expression of one of the genes.

The Examiner provides the rationale for the rejection by outlining the general formula of the constructs taught by Baetscher in the Office Action mailed on May 15, 2006 ("the 2006 Office Action"). Of these, the only constructs that include three markers, namely, a negative selection marker, a positive selection marker, and a reporter gene, are those placed within the context of a retroviral vector. The Examiner, at pages 3-5 of the 2006 Office Action summarizes the structures of Baetscher's constructs that include both positive and negative selection markers and the reporter gene as follows:

> Splice acceptor—IRES—positive selection—negative selection—STOP—***promoter***—reporter;
>
> Splice acceptor—IRES—Neo-HSV-TK—STOP—***promoter***—Ampicillin; and
>
> Splice acceptor—IRES—reporter—negative marker—STOP—***promoter***—positive marker. (Emphasis added.)

Again, each of the constructs includes a promoter within the construct to drive

expression of either the positive selection marker or the reporter, but a construct having a negative selection marker, positive selection marker, and reporter gene under the control of a host cellular promoter after contact with the host cell is never taught by Baetscher.

In contrast, Appellant's claimed constructs require that all three elements (i.e., the positive and negative selectable markers and the reporter gene) be under the control of an endogenous regulatory element in the host cell. Nowhere does the Examiner provide evidence that Baetscher teaches a construct having all three elements where all three elements are promoterless.

Appellant also notes, for the record, that there are inconsistencies in the Examiner's position, which despite Appellant's requests for an explanation remain unaddressed by the Examiner. For example, the Examiner states:

> [I]n order to get expression of the reporter, a promoter element must be operatively linked to the reporter gene. Thus the construct taught by Baetscher et al can be further visualized as having the following general formula:
>
> splice acceptor site—IRES—positive selection—negative selection—STOP—Promoter—reporter. (Page 4, the 2006 Office Action)

The Examiner then goes on to characterize Baetscher as teaching a construct having a splice acceptor site—IRES—positive selection—negative selection—reporter, all under the same endogenous promoter of "a host cellular gene" (Page 6, the 2006 Office Action). The Examiner does not provide any explanation for the Office's interpretation of Baetscher or the inconsistencies in the Examiner's position throughout

the 2006 Office Action.

In sum, all evidence of record indicates that Baetscher does *not* teach a nucleic acid construct that includes a negative selection marker, a positive selection marker, and a reporter gene where all three elements are integrated into the genome of a host cell and responsive to one or more endogenous regulatory elements in the host cell as recited in independent claim 83. In the absence of any evidence to the contrary, Appellant submits that the arguments set forth by the Examiner do not satisfy the legal standard for anticipation, as outlined above, and respectfully requests that the Board reverse the rejection of claims 83, 84, and 88-94 under 35 U.S.C. § 102(b) over Baetscher.

Claims 95-96

Claims 95-96 depend from claim 83 and are directed to a cell that includes the promoterless constructs of claims 83, 84, or 85. Claims 95-96 are also rejected for anticipation by Baetscher. Appellant's traverse this aspect of the rejection on the basis that the Examiner's characterization of Baetscher is erroneous and inconsistent.

As described above for the claims featuring nucleic acids and vectors, Baetscher never teaches a construct having a negative selection marker, positive selection marker, and reporter gene, all three of which are promoterless and under the control of a host cell regulatory element, as recited in Appellant's pending claims.

With regard to the cell of claims 95 and 96, not only does Baetscher fail to teach

all of the limitations of the nucleic acids or vectors but Baetscher also fails to teach a cell that includes a vector having a negative selection marker, a positive selection marker, and a reporter gene where all three elements are integrated into the genome of the cell and responsive to one or more endogenous regulatory elements in the cell as recited in claims 95 and 96.

Appellant submits that Baetscher's teachings fail to describe each and every element of claims 95 and 96 and, by definition, do not satisfy the legal standard for anticipation. Appellant respectfully requests that the Board reverse the rejection of claims 95 and 96 under 35 U.S.C. § 102(b) over Baetscher.

2. The Obviousness Rejections

The Legal Standard for Obviousness Under 35 U.S.C. § 103(a)

A claimed invention is unpatentable if the differences between it and the prior art are such that the claimed subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *See* 35 U.S.C. § 103(a) (2003). Correspondingly, the conclusion regarding obviousness of a claimed invention is based upon the following four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations of nonobviousness (*e.g.,* commercial success, long-felt but unsolved needs,

failure of others). *See McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1368 (Fed. Cir 2003) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)); *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124 (Fed. Cir. 2000) (same); *Ex Parte Crinion*, No. 2001-0210, 2002 WL 31257831, at *2 (Bd. Pat. App. & Interf. 2001) (same); MPEP § 2141.

Three criteria are required to establish a *prima facie* case of obviousness:

First, "[t]here must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor."(s*ee Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000); MPEP § 2143.01). Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. *In re Kahn*, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006) (discussing rationale underlying the motivation-suggestion-teaching test as a guard against using hindsight in an obviousness analysis). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007). Second, there must be a reasonable expectation of success that modification or combination of the prior art will achieve the

claimed invention. MPEP § 2143.02. Third, the prior art reference(s) must teach or suggest all the claim limitations. *See* MPEP § 2143.03.

Claims 85-87, and 97-109 Are Not Obvious Over Baetscher in Combination with MPEP § 2144.04 (VI)(C)*, Zambrowicz, or Massie*

Claims 85-87, and 97-109 stand rejected under 35 U.S.C. § 103 for obviousness over Baetscher in view of MPEP § 2144.04 (VI)(C), Zambrowicz, or Massie. Appellant traverses the rejection because the Examiner's basis for the obviousness rejection does not satisfy the third criteria for a *prima facie* case of obviousness, as provided above, namely, that the prior art references must teach of suggest all the claim limitations.

In rejecting the claims, the Examiner relies on its § 102(b) grounds for rejecting claims 85-87, and 97-109 for obviousness. The secondary references are merely cited for showing that rearrangement of parts is an obvious modification (MPEP § 2144.04 (VI)(C)), that a recombinase site can be included in a nucleic acid construct (Zambrowicz), and that a transactivator can be included in a nucleic acid construct (Massie). Neither Baetscher nor the secondary references teach or suggest a nucleic acid construct, a vector, or a cell that includes a negative selection marker, a positive selection marker, and a reporter gene where all three elements are responsive to one or more endogenous regulatory elements in the host cell. Therefore, the references either alone or combined cannot render claims 85-87, and 97-109 obvious. Appellant respectfully requests that this rejection be overturned.

Appellant separately addresses this ground of rejection as it applies to each of the references.

Claim 85

Claim 85 is rejected for obviousness over Baetscher in view of MPEP § 2144.04 (VI)(C). The Examiner has maintained the rejection because, according to the Examiner, Baetscher teaches all of the elements of the claimed nucleic acids and the cited passage of the MPEP § 2144.04 (VI)(C) states that the rearrangement of parts is an obvious matter of design choice unless the variation modifies the operation of the device. Claim 85, which depends from claim 83, includes limitations that are not taught by Baetscher, regardless of order or orientation. Therefore, claim 85 is not obvious over the combination of Baetscher with MPEP § 2144.04 (VI)(C).

As described above, claim 85 includes the following: a nucleic acid molecule having a positive selection marker, a negative selection marker, and a reporter gene all of which are integrated into the genome of at least one host cell and responsive to one or more endogenous regulatory elements in the cell. Baetscher does not teach a vector having all three elements responsive to an endogenous host cell regulatory element. The citation of MPEP § 2144.04 (VI)(C), with respect to the arrangement of elements in the claims, does not apply to the claims as currently amended because the elements themselves are not taught by Baetscher, regardless of the arrangement. Thus, Appellant

respectfully requests that the Board reverse the rejection of the obviousness rejection, as it pertains to claim 85.

Claims 87 and 106

Claims 87 and 106 are rejected for obviousness over Baetscher in view of Zambrowicz. In maintaining the rejection, the Examiner states that Baetscher teaches all of the elements of the claimed nucleic acids, as described in the § 102(b) rejection, but not the specific use of recombinase sequences in their nucleic acids. The Examiner states that Zambrowicz teaches the construction of gene trap vectors that include splice acceptor sites, IRES elements, and positive/negative selectable marker genes and further teaches the use of recombinase sites within the gene trap cassette. Therefore, the combination of Baetscher with Zambrowicz would, according to the Examiner, render claims 87 and 106 obvious.

Claim 87 depends from claim 83 and features all of the elements of claim 83, as described above, and further includes a recombinase signal sequence. Claim 106 depends from claim 97 and features all of the elements of claim 97 and further includes a recombinase signal sequence. As described in detail above in response to the § 102(b) rejection, Baetscher does not teach all of the limitations of independent claims 83 or 97, or the claims that depend therefrom, and Zambrowicz fails to remedy this deficiency.

Thus, Appellant respectfully requests that the Board reverse the obviousness rejection as it pertains to claims 87 and 106.

Claims 86, 97-105, and 107-109

Claims 86, 97-105, and 107-109 are rejected for obviousness over Baetscher in view of Massie. In setting forth the rejection, the Examiner states that Baetscher teaches all of the elements set forth in the claims with the exception of a transactivator polypeptide incorporated into a cassette or vector but that Massie teaches a cassette and a vector that includes the tetracycline transactivator. Therefore, according to the Examiner, the ordinary skilled artisan would have combined the teachings of Baetscher with Massie to arrive at the present invention. Appellant respectfully disagrees.

Claim 86, which depends from claim 83, features all of the elements of claim 83, as described above, and further includes a nucleic acid encoding a transactivator polypeptide that is incorporated into the cassette or vector.

Independent claim 97 and dependent claims 98-105 and 107-108 feature a vector that includes a positive selection marker, negative selection marker, and a nucleic acid encoding the transactivator polypeptide, all of which are integrated into the genome of a host cell and responsive to one or more endogenous regulatory elements in the cell.

Claim 109 features a cell that includes a cassette having a positive and negative selection marker and a nucleic acid segment encoding a transactivator polypeptide, which

is incorporated into the cassette. The cassette is integrated into the genome of the cell and the positive and negative selection markers and the nucleic acid segment encoding a transactivator polypeptide are responsive to one or more endogenous regulatory elements in the cell. The cell also includes a nucleic acid that includes a promoter operably linked to an element that is directly responsive to the transactivator polypeptide.

As acknowledged by the Examiner, Baetscher does not describe any constructs or cells that include a transactivator polypeptide. As is the case for the previous claims, Baetscher does not teach all of the elements of the claims and Massie fails to remedy this deficiency. Massie describes adenovirus vectors that include a transactivator polypeptide, however, none of Massie's constructs include a transactivator polypeptide that is *integrated into the genome of a host cell and responsive to one or more endogenous regulatory elements in the cell.* Massie teaches the use of a tetracycline-regulated promoter to generate recombinant adenoviruses to express proteins that are cytotoxic or that interfere with adenovirus replication. Massie describes the use of the recombinant adenovirus to produce the toxic proteins by either coexpression of the virus with a second vector that expresses the transactivator (tTA) under the control of a CMV promoter (see page 2292) or by transducing the virus into cell lines that already stably express the tTA under the control of the CMV promoter (see page 2290, Materials and Methods). Massie does not teach a vector or cell in which the expression of the tTA is regulated by an endogenous regulatory element in the host cell. The very purpose of Massie is to

maximize expression of the tTA, not to connect tTA expression to endogenous elements within the host cell that may or may not be activated by stimulatory elements. Massie does not teach any type of construct or cell for examining host cell regulatory element controlled expression of the tTA protein or the selectable markers in the vector. Therefore, taken alone or together, the references fail to teach or suggest all of the limitations of claims 86, 97-105, and 107-109 and Appellant respectfully requests that the Board reverse the obviousness rejection as it applies to these claims.

Conclusion

Appellant respectfully requests that the Board reverse the Examiner's rejection of pending claims 83-109.

Appellant notes that a check for $270.00 in payment of the fee required by 37 C.F.R. § 41.20(b)(2) was paid on July 1, 2008.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: December 30, 2008

Paul T. Clark
Reg. No. 30,162

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Appendix of Claims on Appeal

83. A nucleic acid including:

(a) a splice acceptor site;

(b) a cassette including in any order a negative selection marker, a positive selection marker, and a reporter gene, wherein said negative selection marker, said positive selection maker, and said reporter gene are integrated into the genome of at least one cell and responsive to one or more endogenous regulatory elements in said at least one cell after said nucleic acid is contacted with a cell.

84. The nucleic acid of claim 83, further comprising an internal ribosome entry site.

85. The nucleic acid of claim 84, including in 5' to 3' orientation,

(a) said splice acceptor site;

(b) said negative selection marker and said positive selection marker;

(c) said internal ribosome entry site; and

(d) said reporter gene; or

(a) said splice acceptor site;

(b) said internal ribosome entry site; and

(c) said negative selection marker, said positive selection marker, and said reporter gene, in any order; or

(a) said splice acceptor site;

(b) said reporter gene;

(c) said internal ribosome entry site; and

(d) said negative selection marker and said positive selection marker; or

(a) said splice acceptor site;

(b) said positive selection marker and said reporter gene, in any order;

(c) said internal ribosome entry site; and

(d) said reporter gene; or

(a) said splice acceptor site;

(b) said negative selection marker and said reporter gene, in any order;

(c) said internal ribosome entry site; and

(d) said positive selection marker.

86. The nucleic acid of claim 83, 84, or 85 further comprising a nucleic acid segment encoding a transactivator polypeptide, wherein said nucleic acid segment encoding a transactivator polypeptide is incorporated in said cassette of said nucleic acid molecule.

87. The nucleic acid of claim 83, 84, or 85 further comprising one or more recombinase signal sequences.

88. The nucleic acid of any one of claims 83, 84, or 85, wherein said negative selection marker is selected from the group consisting of Hprt, gpt, HSV-tk, diphtheria toxin, ricin toxin, and cytosine deaminase.

89. The nucleic acid of any one of claims 83, 84, or 85, wherein said positive selection marker is neomycin resistance, hygromycin resistance, histidinol resistance, xanthine utilization, Zeocin resistance, bleomycin resistance, or the presence of green fluorescence protein.

90. The nucleic acid of any one of claims 83, 84, or 85, wherein the reporter gene encodes an enzyme.

91. The nucleic acid of claim 90, wherein said enzyme is selected from the group consisting of secreted alkaline phosphatase, β-galactosidase, luciferase, and green fluorescent protein.

92. A vector that includes the nucleic acid of claim 83, 84, or 85.

93. The vector of claim 92, wherein said vector is a retroviral vector.

94. The vector of claim 92, further including an integration sequence.

95. A cell including the vector of claim 92.

96. The cell of claim 95, wherein said cell is responsive to one or more stimulatory agents.

97. A vector comprising a nucleic acid segment that includes a positive selection marker, a negative selection marker, and a nucleic acid encoding a transactivator polypeptide, wherein said positive selection marker, said negative selection marker, and said nucleic acid encoding said transactivator polypeptide are integrated into the genome

of at least one host cell and responsive to one or more endogenous regulatory elements in said at least one cell after said vector is contacted with a cell.

98. The vector of claim 97, wherein said cassette further comprises an internal ribosome entry site.

99. The vector of claim 97, wherein said negative selection marker is selected from the group consisting of Hprt, gpt, HSV-tk, diphtheria toxin, ricin toxin, and cytosine deeaminase.

100. The vector of claim 97, wherein said positive selection marker is neomycin resistance, hygromycin resistance, histidinol resistance, xanthine utilization, Zeocin resistance, bleomycin resistance, or the presence of green fluorescence protein.

101. The vector of claim 97, wherein said nucleic acid segment further comprises a reporter gene.

102. The vector of claim 101, wherein said reporter gene is operably linked to a host cellular gene after said vector is contacted with a cell.

103. The vector of claim 101, wherein the reporter gene encodes an enzyme.

104. The vector of claim 103, wherein said enzyme is selected from the group consisting of secreted alkaline phosphatase, β-galactosidase, luciferase, and green fluorescent protein.

105. The vector of claim 97, wherein said transactivator polypeptide is a tetracycline regulator unit (tTA).

106. The vector of claim 97, further including one or more recombinase signal sequences.

107. A cell including the vector of claim 97.

108. The cell of claim 107, wherein said cell is responsive to one or more stimulatory agents.

109. A cell including (i) a cassette which includes a positive selection marker, a negative selection marker, and a nucleic acid segment encoding a transactivator polypeptide, wherein said cassette is integrated into the genome of the cell and said

positive selection marker, negative selection marker, and nucleic acid segment encoding a transactivator polypeptide are responsive to one or more endogenous regulatory elements in said cell and (ii) a nucleic acid which includes a promoter operably linked to a responsive element that is directly responsive to said transactivator polypeptide.

Evidence Appendix

None

Related Proceedings Appendix

None

DATED **2008**

BTG INTERNATIONAL LIMITED

- and –

BIONAUT PHARMACEUTICALS INC

ASSIGNMENT

of US patent 5922601; US patent applications 10/029471; 11/0183919;11/653076; 11/219636; 11/254246; 11/219638; 11/989362; 12/087459 & PCT application PCT/GB08/000320 and corresponding rights

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BTG International Ltd
10 Fleet Place
Limeburner Lane
London EC4M 7SB

BTG

This Assignment is made as a Deed on 2008

between:

(1) **BTG INTERNATIONAL LIMITED** whose company registration number in England and Wales is 2664412 and whose registered address is at 10 Fleet Place, Limeburner Lane, London, EC4M 7SB, England ("BTG"), and

(2) **BIONAUT PHARMACEUTICALS INC** of 16 Rustic Road, Stoneham, MA 02180, USA ("Bionaut").

Whereas:-

A. BTG is the proprietor and/or beneficial owner of the patent applications and know-how, details of which are set out in the Schedule to this Agreement, (all such patent applications and know-how, are herein together called the "IPR").

B. Pursuant to an Asset Acquisition and Revenue Sharing Agreement ("The Asset Acquisition Agreement") made between Bionaut and BTG dated 28 February 2007, BTG has agreed that the IPR shall be assigned to Bionaut on the terms hereinafter set forth.

Now it is hereby agreed as follows:-

1. BTG hereby assigns to Bionaut all its right, title, and interest in the IPR, free from encumbrances, except for encumbrances disclosed or otherwise known to Bionaut, and together with all rights transferable with such encumbrances.

2. This Deed shall be read and construed in accordance with, and governed by, English law, and the parties submit to the jurisdiction of the English Courts.

In witness whereof this document has been executed and delivered as a deed on the date first written above.

BTG6228 SCHEDULE OF PATENTS

BTG6228 - HIGH EFFICIENCY GENE TRAP SELECTION OF REGULATED GENETIC LOCI									
Internal reference	Country	Filing date	Filing number	Publication date	Publication number	Grant date	Grant number	Expiry	Current Status
622803US02	USA	16/SEP/1996	08/716854			13/JUL/1999	5922601	19/JAN/2015	GRANTED

BTG6228 - COMPOSITIONS AND METHODS FOR THE DISCOVERY AND SELECTION OF BIOLOGICAL INFORMATION									
Internal reference	Country	Filing date	Filing number	Publication date	Publication number	Grant date	Grant number	Expiry	Current Status
622804AU01	AUSTRALIA	26/OCT/2001	2002230752	06/MAY/2002	3075202	19/JUN/2008	2002230752	26/OCT/2021	GRANTED
622804CA01	CANADA	26/OCT/2001	2426896	02/MAY/2002	2426896			26/OCT/2021	PUBLICATION
622804EP01	EUROPE	26/OCT/2001	01984619.5	09/OCT/2002	1246946			26/OCT/2021	PUBLICATION
622804JP01	JAPAN	26/OCT/2001	2002-537853	24/SEP/2004	2004-528815			26/OCT/2021	PUBLICATION
622804US03	USA	25/OCT/2001	10/029471	02/JAN/2003	2003-0003519			27/OCT/2020	PUBLICATION

BTG6228 - ANTI-NEOPLASTIC AGENTS, COMBINATION THERAPIES AND RELATED METHODS									
Internal reference	Country	Filing date	Filing number	Publication date	Publication number	Grant date	Grant number	Expiry	Current Status
622805US01	USA	20/DEC/2004	11/018399	10/NOV/2005	2005-0250709			20/DEC/2024	PUBLICATION

BTG6228 - TREATMENT OF REFRACTORY CANCERS USING NA+/K+ ATPASE INHIBITORS									
Internal reference	Country	Filing date	Filing number	Publication date	Publication number	Grant date	Grant number	Expiry	Current Status
622806EP01	EUROPE	02/SEP/2005	05796526.1	23/MAY/2007	1786440			02/SEP/2025	PUBLICATION
622806US01	USA	01/SEP/2005	11/218332	22/JUN/2006	2006-0135468			01/SEP/2025	PUBLICATION
622806US03	USA	12/JAN/2007	11/653076	31/JAN/2008	2008-0027010			01/SEP/2025	PUBLICATION

BTG6228 - COMBINATORIAL CHEMOTHERAPY TREATMENT USING NA+/K+ ATPASE INHIBITORS									
Internal reference	Country	Filing date	Filing number	Publication date	Publication number	Grant date	Grant number	Expiry	Current Status
622807EP01	EUROPE	02/SEP/2005	05796380.3	30/MAY/2007	1789090			02/SEP/2025	PUBLICATION
622807US01	USA	02/SEP/2005	11/219636	22/JUN/2006	2006-0135441			02/SEP/2025	PUBLICATION
622807US02	USA	24/MAY/2006	11/441396	10/MAY/2007	2007-0105789			02/SEP/2025	PUBLICATION

BTG6228 - USE OF NA+/ K+-ATPASE INHIBITORS AND ANTAGONISTS THEREOF									
Internal reference	Country	Filing date	Filing number	Publication date	Publication number	Grant date	Grant number	Expiry	Current Status
622808EP01	EUROPE	18/OCT/2005	05812216.9	01/AUG/2007	1812010			18/OCT/2025	PUBLICATION
622808US01	USA	18/OCT/2005	11/254246	22/JUN/2006	2006-0135443			18/OCT/2025	PUBLICATION

BTG6228 - PANCREATIC CANCER TREATMENT USING NA+/K+ ATPASE INHIBITORS									
Internal reference	Country	Filing date	Filing number	Publication date	Publication number	Grant date	Grant number	Expiry	Current Status
622809EP01	EUROPE	02/SEP/2005	05794315.1	20/JUN/2007	1796688			02/SEP/2025	PUBLICATION
622809US01	USA	02/SEP/2005	11/219638	22/JUN/2006	2006-0135442			02/SEP/2025	PUBLICATION
622809US02	USA	24/MAY/2006	11/441397	10/MAY/2007	2007-0105790			02/SEP/2025	PUBLICATION

BTG6228 - MODULATORS OF HYPOXIA INDUCIBLE FACTOR-1 AND RELATED USES FOR THE TREATMENT OF OCULAR DISORDERS									
Internal reference	Country	Filing date	Filing number	Publication date	Publication number	Grant date	Grant number	Expiry	Current Status
622810EP01	EUROPE	01/AUG/2006	06789280.2	11/JUN/2008	1928470			01/AUG/2026	PUBLICATION
622810US01	USA	01/AUG/2006	11/989362					01/AUG/2026	FILING

BTG6228 - MODULATORS OF HYPOXIA INDUCIBLE FACTOR-1 AND RELATED USES									
Internal reference	Country	Filing date	Filing number	Publication date	Publication number	Grant date	Grant number	Expiry	Current Status
622811AU01	AUSTRALIA	09/JAN/2007	2007205092	19/JUL/2008	2007205092			09/JAN/2027	PUBLICATION
622811BR01	BRAZIL	09/JAN/2007	PCT/US07/000340					09/JAN/2027	FILING
622811CA01	CANADA	09/JAN/2007	PCT/US07/000340					09/JAN/2027	FILING
622811CN01	CHINA	09/JAN/2007	PCT/US07/000340					09/JAN/2027	FILING
622811EP01	EUROPE	09/JAN/2007	07717832.5	24/SEP/2008	1971618			09/JAN/2027	PUBLICATION
622811GB01	UNITED KINGDOM	09/JAN/2007	0812342.4					09/JAN/2027	FILING
622811IN01	INDIA	09/JAN/2007	5754/DELNP/2008					09/JAN/2027	FILING
622811JP01	JAPAN	09/JAN/2007	PCT/US07/000340					09/JAN/2027	FILING
622811MX01	MEXICO	09/JAN/2007	MX/a/2008/008608					09/JAN/2027	FILING
622811US02	USA	09/JAN/2007	12/087459					09/JAN/2027	FILING

BTG6228 - MODULATORS OF HYPOXIA INDUCIBLE FACTOR-1 AND RELATED USES (OXIME ANALOGUES OF BP228)									
Internal reference	Country	Filing date	Filing number	Publication date	Publication number	Grant date	Grant number	Expiry	Current Status
622812W001	INTERNATIONAL	31/JAN/2008	PCT/GB08/000320	07/AUG/2008	WO2008/093086			31/JAN/2028	PUBLICATION

Executed as a Deed by)
BTGINTERNATIONAL LIMITED)
in a manner legally binding upon it)

Director/Authorised Signatory

Witnessed by:

Signature of witness

Name of witness: LINDA STENBERG

Address of witness: FLAT 3

31 BECHEAD AVENUE

SW16 1QJ

Executed as a Deed by)
BIONAUT PHARMACEUTICALS INC)
in a manner legally binding upon it)

Director/Authorised Signatory

DATED 2008

BTG INTERNATIONAL LIMITED

- and –

BIONAUT PHARMACEUTICALS INC

ASSIGNMENT

of US patent 5922601; US patent applications 10/029471; 11/0183919;11/653076; 11/219636; 11/254246; 11/219638; 11/989362; 12/087459 & PCT application PCT/GB08/000320 and corresponding rights

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